REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks pursuant to and consistent with 37 C.F.R § 1.112 are respectfully requested. The Office Action Summary correctly indicates that claims 1-19 are pending in this application. Claims 15, 16, 18, and 19 have been withdrawn as directed to non-elected subject matter.

Claims 1, 10 and 14 been amended herein. Claims 6-9 have been deleted, as the subject matter of these claims was redundant in light of the amendment to claims 1. Applicants reserve the right to file a Divisional or Continuation Application directed to any matter canceled by way of the present Amendment. Basis for the amendments to the claims may be found throughout the specification and claims as-filed, especially on page 3, lines 10-19 and page 3, line 36 to page 4, line 15. Thus, no improper new matter has been introduced by way of this Amendment.

Objections to the Specification

The specification stands objected to because it purportedly lacks most of the appropriate section headings. The specification has been amended herein to include the appropriate section headings. Thus, Applicants respectfully submit that this objection has been obviated.

In addition, Applicants take this opportunity to submit the Abstract of the Disclosure, attached hereto.

Objections to the Claims

Claim 6 stands objected to for reciting "cytoxin", which should purportedly be spelled "cytotoxin". Claim 6 has been canceled by way of the present Amendment. Thus, Applicants respectfully submit that this objection is mooted.

Priority

The specification is objected to because Applicant has purportedly failed to comply with one or more conditions for receiving the benefit of an earlier filing dated under 35 US.C. § 120. The specification has been amended herein to recite specific references to the prior applications from which this application should receive priority benefit. Thus, Applicants respectfully submit that this objection has been obviated.

Rejections under 35 U.S.C. § 112, Second Paragraph and 35 U.S.C. § 101

Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite because, although claim 14 provides for the use of the agent, the claim purportedly fails to set forth any steps involved in the method process. Claim 14 also stands rejected under 35 U.S.C. § 101 because the claimed recitation of a use without setting forth any steps involved in the process purportedly results in an improper definition of a process. Claim 14 has been amended herein to recite "a method of treating cancer comprising administering to a patient an agent according to claim 1". Applicants respectfully submit that, as amended, claim 14 now sets forth proper method steps. Further, as amended, claim 14 now appears in proper U.S. format. Thus, Applicants that

the rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101 have been obviated.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 14 and 17 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while providing enablement for methods of treating cancer with an agent of claim 1, where the agent is a multimeric α-lactalbumin conjugated with a targeting protein such as an antibody, purportedly fails to reasonably provide enablement for methods of treating cancer with any agent within the scope of claim 1. Applicants respectfully traverse this rejection.

The Office Action states that the specification is enabled only when the multimeric α-lactalbumin is coupled to a targeting protein such as an antibody. Applicants respectfully submit that this is not the case. The Examples in the specification clearly demonstrate that this coupling is not necessary, as simply iodine labeled multimeric α-lactalbumin targeted nuclei of cancer cells. The present specification discloses that the multimeric α-lactalbumin itself acts as a targeting agent, entering the nuclei of cancer cells. The multimeric α-lactalbumin of the present invention is, in effect, a targeting protein, which can carry other reagents, such as labels, into the nucleus. Thus, it is entirely reasonable to predict that multimeric α-lactalbumin could be used to target therapeutic agents, such as cytotoxins, and also therapeutics antibodies to the cells.

The Office Action cites a paper by R.K. Jain (*Scientific American*, 271:58-65 (1994)) which purportedly discloses that there is a need to show *in vivo* data in the case of

anti-cancer effects. Applicants respectfully disagree. Jain discloses that some reagents, which kill cells in dishes, are enabled to penetrate solid tumors *in vivo*. However, in the present invention as discussed above, the targeting ability of the multimeric α-lactalbumin has been demonstrated. Thus it is reasonable to predict that the problems encountered by other reagents in accessing tumor cells in sufficient concentrations to be toxic would not apply to the claims of the present invention. Furthermore, Applicants have begun *in vivo* work with iodine labeled multimeric α-lactalbumin in rats. The data has shown that the administration prolongs survival. Applicants respectfully submit a copy of a draft paper entitled "HAMLET Induces Apoptosis in Glioblastoma Cells and Delays Tumour Progression *In Vivo*". This draft paper provides further data supporting Applicants assertions. This data could be submitted to the Examiner in the form of a 37 C.F.R. § 132 Declaration, if necessary.

However, Applicants submit that if the Examiner agrees that the specification is enabling for a combination of multimeric α-lactalbumin in a targeting antibody, then the full scope of the claims is enabled in light of the discussion above and in view of the fact that multimeric α-lactalbumin is itself a targeting moiety.

Thus, in light of the above remarks, Applicants respectfully submit that this rejection has been obviated.

Rejections under 35 U.S.C. § 102(b)

Sabharwal *et al.*

Claims 1 and 11-13 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Sabharwal *et al.* (WO 96/04920) as evidenced by Kuwajima (*FASEB Journal*, 10:102-109 (1996)). Sabharwal *et al.* is cited for purportedly disclosing multimeric α-lactalbumin, which is a compound which binds calcium ion, as evidenced by the teaching of Kuwajima.

Respectfully, "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claims". Jamesbury Corp. v. Litton Industrial Products, Inc., 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). Sabharwal *et al.* do not teach or suggest the claimed invention as amended.

Claim 1 has been amended herein to define the term "further reagent" as being "selected from the group consisting of a cytotoxin, a chemotherapeutic agent, a microbial toxin, a therapeutic antibody and a label which may be visualized and a radiolabel". Applicants respectfully submit that the cited reference does not disclose all of the elements of the rejected claims, as amended.

Sabharwal *et al.*, as evidenced by Kuwajima, disclose the inclusion of calcium in multimeric α-lactalbumin complexes. As disclosed in these references, the calcium presence stabilized a particular form of the multimeric α-lactalbumin. However, although the calcium had a stabilizing effect, it was not intended as a therapeutic agent in the context of the cited references. As amended, independent claim 1 now recites specific reagents

which are not disclosed by Sabharwal *et al.* Thus, Applicants submit that this rejection under 35 U.S.C. § 102(b) has been obviated.

Thus, as the Sabharwal *et al.* reference does not teach every element of the invention as claimed, the reference cannot anticipate the invention. Accordingly, Applicant respectfully requests that the rejection based on the Sabharwal *et al.* reference and made under 35 U.S.C. § 102(b) be withdrawn in light of the above arguments.

Hakansson *et al.*

Claim 1 stands rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Hakansson *et al.* (*Proc. Natl. Acad. Sci., USA*, 92:8064-8068 (1995)) as evidenced by Kuwajima. Hakansson *et al.* is cited for purportedly disclosing multimeric α-lactalbumin.

As discussed above, claim 1 has been amended to define the term "further reagent" as being "selected from the group consisting of a cytotoxin, a chemotherapeutic agent, a microbial toxin, a therapeutic antibody and a label which may be visualized and a radiolabel". Applicants respectfully submit that the cited reference does not disclose all of the elements of the rejected claims, as amended.

Accordingly, Applicant respectfully requests that the rejection based on the Hakansson *et al.* reference and made under 35 U.S.C. § 102(b) be withdrawn in light of the above arguments.

Rejections under 35 U.S.C. § 103(a)

Ming

Claims 1 and 8 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Ming (*Magnetic Resonance in Chemistry*, 31:S104-S109 (1993)). Ming is cited for purportedly disclosing the substitution of calcium ion with ytterbium ion. Ytterbium ion is considered to be a labeling agent, because purportedly Ming discloses its use as a paramagnetic probe in NMR spectroscopy. Although Ming fails to teach multimeric α-lactalbumin complexed with ytterbium ion, the Office Action states that it would be obvious to the skilled artisan at the time the invention was made to label multimeric α-lactalbumin with ytterbium ion.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires *enter alia*, consideration of two factors: [1] whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and [2] whether the prior art would also have revealed that in so making or carrying out those of ordinary skill in the art would have a reasonable expectation of success. *See, In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

It is respectfully submitted that a legally sufficient *prima facie* case of obviousness has not been adduced because the cited reference does not teach, suggest or provide motivation for the claimed invention, let alone provide the skilled artisan with an expectation of success.

Ming discloses the substitution of calcium with ytterbium. As amended, claim 1 recites a "further reagent" as being "selected from the group consisting of a cytotoxin, a chemotherapeutic agent, a microbial toxin, a therapeutic antibody and a label which may be visualized and a radiolabel". As amended, the claimed invention does not cover calcium as a reagent. Applicants submit that it would not occur to the skilled artisan to replace any of the other claimed reagents with ytterbium. Ming fails to provide any motivation for the skilled artisan to look for an alternative to calcium. Thus, the cited reference fails to provide the skilled artisan with an expectation of success in practicing the claimed invention. It is not reasonable to suppose that the skilled artisan would be led to the claimed invention by the cited reference.

In addition, with regard to the present invention, Applicants have been the first to discover that the multimeric α-lactalbumin itself can act as a targeting moiety. There is no need to use any additional targeting antibodies to ensure that the reagent attacks only the tumor and cells when the present invention is used. The present invention discloses methods of using multimeric α-lactalbumin as a carrier to assist in targeting other reagents. Because this targeting effect has not been disclosed in the cited reference, the use of multimeric α-lactalbumin in this way cannot be considered to be obvious.

In light of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Hakansson *et al.* in view of Blair and Ghose

Claims 1-4, 6, 7, 11, 14 and 17 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Hakansson *et al.* in view of Blair and Ghose (*J. of Immunological Methods*, 59:129-143 (1983)). Hakansson *et al.* is cited for purportedly disclosing multimeric α-lactalbumin and for purportedly disclosing that multimeric α-lactalbumin is a toxin to cancer cells and immature cells. Although Hakansson *et al.* failed to disclose multimeric α-lactalbumin conjugated to a second agent, such as an antibody, the Office Action states it would be obvious to the skilled artisan to combine the multimeric α-lactalbumin disclosed by Hakansson with the conjugation of cytotoxic agents targeting molecules purportedly disclosed by Blair and Ghose. Applicants respectfully traverse this rejection.

As above, with regard to the present invention, Applicants have been the first to discover that the multimeric α-lactalbumin itself can act as a targeting moiety. There is no need to use any additional targeting antibodies to ensure that the reagent attacks only the tumor and cells when the present invention is used. The present invention discloses methods of using multimeric α-lactalbumin as a carrier to assist in targeting other reagents. Because this targeting effect has not been disclosed in the cited references, the use of multimeric α-lactalbumin in this way cannot be considered to be obvious.

In light of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Hakansson *et al.* in view of Puri *et al.*

Claims 1, 5 and 11 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Hakansson *et al.* in view of Puri *et al.* (U.S. Patent 5,614,191). Although Hakansson *et al.* fails to disclose multimeric α-lactalbumin as part of a fusion protein fused to a second protein or polypeptide, the Office Action states it would be obvious to the skilled artisan to modify the α-lactalbumin of Hakansson *et al.* to make it a fusion protein as disclosed in Puri *et al.*

As above, with regard to the present invention, Applicants have been the first to discover that the multimeric α-lactalbumin itself can act as a targeting moiety. There is no need to use any additional targeting antibodies to ensure that the reagent attacks only the tumor and cells when the present invention is used. The present invention discloses methods of using multimeric α-lactalbumin as a carrier to assist in targeting other reagents. Because this targeting effect has not been disclosed in the cited references, the use of multimeric α-lactalbumin in this way cannot be considered to be obvious.

In light of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Hakansson *et al.* in view of Johnstone and Thorpe

Claims 1 and 8-10 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Hakansson *et al.* in view of Johnstone and Thorpe (*Immunochemistry in Practice*, Blackwell Scientific Publications, Oxford:113-130 (1987)) and also in view of Goers (*J Immunochemical Techniques Laboratory Manual*, Academic Press, New York:69-

79 (1993)). As above, Hakansson *et al.* is cited for purportedly teaching multimeric α-lactalbumin. Johnstone and Thorpe and Goers are cited for purportedly disclosing the radiolabeling of proteins and demonstrating how to radiolabel with ^{125}I, ^{14}C and ^{35}S. Goers is cited for purportedly disclosing the labeling of antibodies and methods of labeling with biotin. The Office Action states that it would have been obvious to the skilled artisan to modify the multimeric α-lactalbumin disclosed by Hakansson *et al.* to make a labeled agent disclosed as disclosed by the secondary references.

The Office Action suggests that labeling of proteins is well know in the art and therefore, the recitation of claim 1 covering labeled multimeric α-lactalbumin is obvious. Applicants respectfully traverse this rejection.

The Applicants have unexpectedly found that, as a result of the fact that multimeric α-lactalbumin specifically target the nucleus of cancer cells, labeled material is particularly useful in cellular assays, as illustrated in the specification. As discussed in the specification, the nuclei of tumor cells can be simply "lit up" using the reagents of the present invention which include a label. This advantage for such materials is quite unexpected because the targeting properties of multimeric α-lactalbumin were not known prior to the claimed invention.

Thus, there would be no motivation for the skilled artisan to modify the multimeric α-lactalbumin of Hakansson *et al.* to comprise a label, because there is no disclosure in any of the cited references teaching that multimeric α-lactalbumin may be used in targeting.

In light of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Respectfully submitted,

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Attachment to Amendment and Reply under 37 C.F.R § 1.111

Marked-up Claims 1, 10, and 14

1. (Amended) An agent comprising a protein complex comprising an oligomeric form of α-lactalbumin (MAL) and a further reagent selected from the group consisting of a cytotoxin, a chemotherapeutic agent, a microbial toxin, a therapeutic antibody and a label which may be visualized and a radiolabel which is combined with MAL such that it is carried into the nucleoplasm of cells which are susceptible to MAL.

10. (Amended) An agent according to claim 1, wherein the radiolabel comprises [9 which has a radioactive label comprising] ^{125}I, ^{14}C or ^{35}S.

14. (Twice Amended) A method of treating cancer comprising administering to a patient an agent according to claim 1 [The use of an agent according to claim 1 in the treatment of cancer].

--ABSTRACT

An agent comprising a protein complex comprising an oligomeric form of α-lactalbumin (MAL) and a further reagent which is combined with MAL such that it is carried into the nucleoplasm of cells which are susceptible to MAL. Agents of the type, where the further reagent is a therapeutic or labelling reagent, can be used in diagnosis and therapy in particular of cancer.--